DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Cheryl Rini
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
130 Waverly St.
Cambridge, MA 02139

RE: NDA 201917
INCIVEK™ (telaprevir) Film Coated Tablets
MA# 54

Dear Ms. Rini,

The Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP) of the U.S. Food and Drug Administration (FDA) has reviewed the James JP M. Branded Story (branded story) (VX11-1111.01) for INCIVEK™ (telaprevir) Film Coated Tablets (Incivek) submitted by Vertex Pharmaceuticals, Inc. (Vertex) under cover of Form FDA-2253. The branded story is misleading because it overstates the efficacy, omits material facts, and minimizes important risk information about the drug product. Thus, the branded story misbrands Incivek in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Incivek.[1]

According to the Indications and Usage section of the FDA-approved product labeling (PI):

> INCIVEK™ (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.
>
> The following points should be considered when initiating treatment with INCIVEK (emphasis original):
>
> - INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors.

Incivek is associated with a number of serious risks. Specifically, Incivek is contraindicated for use in women who are or may become pregnant, men whose female partners are pregnant, when co-administrated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, and when combined with drugs that strongly induce CYP3A which may lead to lower exposure and loss of efficacy of Incivek. The PI also contains warnings and precautions regarding use in pregnancy, serious skin reactions, rash, anemia, drug interactions, laboratory tests, and hepatic impairment. The most common adverse reactions in adult patients treated with Incivek were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus. In addition, because Incivek must be used in combination with peginterferon alfa and ribavirin, the risks associated with these drugs also apply to combination therapy with Incivek.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The branded story is an account of James' life and medical history since being diagnosed with hepatitis C. Specifically, the story describes James' diagnosis of stage 3 cirrhosis and subsequent null response after 6-months of treatment with pegylated-interferon and ribavirin combination therapy. After treatment with Incivek combination therapy, the story claims:

- "And six months after treatment ended, I found out I'd cleared the virus. That made me feel so good. I was so happy to know I'd be around a little longer to see my son grow up." [page 5]
- ". . .I'm cleared, I can take my son to the batting cage. We go sailing on my boat and take nice vacations. I even retired from the railroad and started a successful cab business, which I really enjoy. I'm loving life." [page 5]

While these claims may be an accurate reflection of James' own experience with hepatitis C and treatment with Incivek, this branded story misleadingly implies that most or all cirrhotic prior null responders infected with hepatitis C will successfully achieve Sustained Virologic Response (SVR) on Incivek combination therapy. FDA is not aware of substantial evidence or substantial clinical experience to support this implication. One patient's treatment response does not constitute substantial evidence. According to the Clinical Studies section of the PI, of the prior null responders with cirrhosis tested in clinical trials, 14% who received

Incivek combination therapy achieved SVR versus 10% in the placebo/PR48 treatment group. These SVR rates are significantly lower than the rates achieved by other populations in clinical trials, and do not support the misleading impression that most or all cirrhotic prior null responders infected with hepatitis C can expect to achieve SVR with Incivek combination treatment. In addition, 50% of treatment-experienced prior null responders in the Incivek treatment group experienced on-treatment virologic failure and 24% experienced relapse. Furthermore, according to the Indications and Usage section of the PI, "A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment."

The claims above also misleadingly overstate the efficacy of Incivek by suggesting that the usual outcome of treatment with Incivek is a positive effect on a patient's interpersonal relationships, physical functioning, work productivity, and overall quality of life. FDA is not aware of substantial evidence or substantial clinical experience to support such effects of Incivek treatment for patients. These claims of treatment benefit require substantial evidence or substantial clinical experience as demonstrated through adequate and well-controlled trial(s) using well-developed instruments that reliably and validly measure the specific concepts at issue. If you have such data to support these claims, please submit them to FDA for review.

Omission of Material Fact

Promotional materials are false or misleading if they fail to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials.

The claims of "cleared" cited above also omit important material information regarding treatment success in clinical trials. Specifically, the term "cleared" misleadingly implies removal of HCV from the body, when this is not the case. Patients with undetectable HCV-RNA levels after therapy may still have replication competent virus. According to the Clinical Studies section of the PI, "SVR in all studies was defined as HCV-RNA less than 25 IU/mL at 24 weeks after the planned end of treatment."

Minimization of Risk Information

Promotional materials are misleading if they suggest that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. Page 5 of the branded story contains the claim, "When the side effects kicked in, I got a rash and lost some hair, but that was nothing." This claim is misleading because it minimizes the risk of rash and alopecia associated with Incivek combination therapy. Specifically, this claim suggests that rash is not a serious side effect, when this is not the case. According to the Warnings and Precautions section of the PI, serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and severe rash have been reported in patients receiving Incivek combination therapy. And while mild to moderate

skin rashes are common with Incivek, they should be followed for progression and development of systemic symptoms. Furthermore, the Incivek Medication Guide cites rash (with or without itching) as a skin reaction that should prompt an urgent call to a healthcare provider because, **"Sometimes these skin rashes and other skin reactions can become severe and require treatment in a hospital"** (bolded emphasis original). We note that an "Important Safety Information" slide deck (VX11-1021.01) was submitted on July 20, 2011 under cover of Form FDA-2253, which Vertex stated would accompany the branded story presentation. However, the presentation of this risk information in the "Important Safety Information" slide deck does not mitigate the misleading minimization of risk information regarding rash cited above.

We also note that the Warnings and Precautions section of the PI states that "INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. Therefore, the prescribing information for peginterferon alfa and ribavirin must be consulted before starting treatment with INCIVEK." (emphasis original). According to the prescribing information for peginterferon alfa and ribavirin, alopecia is a common adverse reaction associated with therapy. Therefore, the implication that this side effect is "nothing" misleadingly minimizes this risk. The minimization of these important risks associated with Incivek combination therapy misleadingly suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the branded story misbrands Incivek in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i).

OPDP requests that Vertex immediately cease the dissemination of violative promotional materials for Incivek such as those described above. Please submit a written response to this letter on or before June 11, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Incivek that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA# 54 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Incivek comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sheetal Patel, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Michael Sauers, MPP
Team Leader
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

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/s/

SHEETAL PATEL
05/25/2012

MICHAEL A SAUERS
05/25/2012